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Differences in the S value between male and female murine model for diagnostic, therapeutic and theragnostic radionuclides

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HIGHLIGHTS

- Murine self-absorbed S values.
- Dosimetry using MOBY phantom.
- Dosimetry of ^{99m}Tc, ^{67}Ga, ^{68}Ga, ^{18}F, ^{223}Ra, ^{166}Ho, ^{90}Y, ^{161}Tb ^{131}I and ^{177}Lu.
- Radiation transport was performed with GATE/Geant4 platform.

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ABSTRACT

The aim of this work was to calculate S values for ^{99}mTc, ^{67}Ga, ^{68}Ga, ^{18}F, ^{223}Ra, ^{166}Ho, ^{90}Y, ^{161}Tb ^{131}I and ^{177}Lu, using a mouse phantom (MOBY) standard and considering the anatomic sizes from males and females, the simulation of radiation transport was performed with GATE/Geant4 platform. This indicates that in the internal dosimetry the use of a customized geometry is relevant for each gender and a standard model is not a good choice.

1. Introduction

Small animals such as rodents have been used for preclinical purposes when new radiopharmaceuticals are developed prior the application in humans, to study several diseases in its natural state. Rodents as rats and mice are widely used in preclinical research studies to develop and test new treatments and imaging methods for human diseases (Gangadaran et al., 2018; Hindorf et al., 2004; Pet et al., 2007; Tuveson and Hanahan, 2011; Vieyra-Reyes et al., 2017). Mice were not used only with experimental purpose, also they have been used as model in ionizing radiation dosimetry and imaging, there are a lot of examples (Taschereau and Chatziioannou, 2007). Taschereau et al. mentioned that is important to quantify accurately the absorbed dose in organs because the effects on a given investigation are hard to predict; however, investigators should be aware of potential perturbations especially when the studied organ receives high absorbed dose and when longitudinal imaging protocols are considered (Taschereau and Chatziioannou, 2007). In this context, the most common method for calculating the absorbed dose to a target region from ionizing radiation emitted from a source region is by Medical Internal Radiation Dose (MIRD) formalism, where absorbed dose is defined as $D = \tilde{A}_h . S(r_k \leftarrow r_h)$, $\tilde{A}_h$ is the cumulated activity in source region and $S(r_k \leftarrow r_h)$ [Gy/Bq*s] is the S value. The absorbed dose per unit cumulated activity was named S value by MIRD in 1965 and it is now very well accepted for internal dosimetry. S values are generally calculated for anatomic models with Monte Carlo method or dose kernels for both animals and humans(Hindorf et al., 2004), because the dosimetry is important in understanding the relationship between absorbed dose and response, which can be translated to preclinical results for humans.

Several analytical phantoms have been considered as anatomic models for the dosimetry which used ellipsoids, spheroids and cylinders as organs, but the evolution of the graphic computing allows to create more realistic mouse phantoms using structures very well defined with the shape of a real organ even with movement such as respiratory motion(Segars et al., 2004). In general, absorbed dose is geometry dependent value, so the S value also, estimation of absorbed dose will be more accurate in a mouse phantom with realistic structures (organs). The use of realistic mouse phantoms as MOBY have been widely used along with Monte Carlo simulations to compute reference dosimetric quantities(Kolbert et al., 2003). The MOBY phantom was developed by

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Segars et al. (2004), it is an example of hybrid phantom, it is based on non-uniform, rational B-spline surfaces, these surfaces allow flexibility in the shapes of the organs, thirty-six regions and three skeletal regions are segmented. The phantom is software controlled by a user-modified parameter file and generates two sets of 3D voxel-based images with specific matrix size of activity and attenuation in the mouse(Larsson, 2011). GEANT 4 is Monte Carlo code to perform ionizing radiation transport, it was used to implement MOBY phantom in its platform GATE(Jan et al., 2004; Taschereau and Chatziioannou, 2007), also MOBY phantom has been implemented in MCNPX v2.7 for preclinical assessments of radiopharmaceuticals (Mohammadi and Kinase, 2011).

The Gallium-67 (^{67}Ga) citrate is widely used as a diagnostic agent of inflammation, infection, cancer, iron deficiency, etc.(Tsan and Scheffel, 1986)(Marti et al., 2011)(Upadhyay et al., 2015)(Vieyra-Reyes et al., 2017). Positron emitters as ^{18}F and ^{68}Ga are also used in small laboratory rodents to visualize and track molecular processes associated with diseases such as cancer, heart disease and neurological disorders in living small animal models of disease(Dam et al., 2016)(Xie and Zaidi, 2013). Lutetium-177 (^{177}Lu) has been widely used as a theragnostic radionuclide, because its medium energy β and gamma emission for pretreatment imaging. Terbium-161 (^{161}Tb) has β emission similar to that of ^{177}Lu, it seems to be a promising therapeutic radionuclide (Champion et al., 2016), also Holmium-166 (^{166}Ho) has been used in targeted therapy. Currently, targeted alfa particle therapy is rapidly developing, it is useful to the irradiation of fewer cancer cells, micrometastases or tumors by an emission of a single alpha particle or by a cascade of heavy alpha particles from close vicinity(Kozempel et al., 2018), the alfa particle emitter Radium-223 (^{223}Ra) has demonstrated to be useful for bone metastases treatment on patients with resistant prostate cancer (Loizaga-Iriarte et al., 2018).

Nevertheless, many diseases specifically affect women or men, this implies that preclinical studies must performed in female or male animal models, in order to ensure accurate dosimetry, it is important to consider the gender due to the influence of the mass, shape and the distances between organs in calculating of S values. For above, the aim of this work was to calculate S values for ^{99m}Tc, ^{67}Ga, ^{68}Ga, ^{18}F, ^{223}Ra, ^{166}Ho, ^{90}Y, ^{161}Tb ^{131}I and ^{177}Lu, using a mouse phantom (MOBY) standard and considering the anatomic sizes from males and females, the simulation of radiation transport was performed with GATE/Geant4 platform.

2. Methodology

2.1. Organ masses

The study was conducted in accordance with approved institutional protocols in agreement with the Principles and Procedures described by the National Institute of Health, Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, in accordance with the Local Ethics Committee(Ochoa Muñoz, 1999). 12 CD-1 mice were used, in two groups: 6 females and 6 males. They were maintained in standard conditions of the animal facility: water and food at a free demand, 50–55% of humidity, temperature set to 22 ± 2 °C, a 12:12 light/dark cycle was used, where light was turned on at 6 o'clock. At 12 weeks old, they were euthanized by CO_2 inhalation method to minimize suffering. Then, heart, spleen, kidneys and liver from each test subject of the female group (FG) and the male group (MG) were dissected, those organs were weighted, and the average mass of each organ was obtained for FG and MG.

2.2. MOBY models and GATE/GEANT4

Using the organ mass obtained and multiplying with its corresponding density from GateMaterials data base, new organ volumes were calculated and rescaled in the parameter file of MOBY software. Then, two models were created: female model (FM) and male model (MM), besides the original phantom. All three models were exported in a 256 × 256 x 739 voxel phantom to perform the simulation and to obtain the S value for each mentioned organ for ^{99m}Tc, ^{67}Ga, ^{68}Ga, ^{18}F, ^{223}Ra, ^{166}Ho, ^{90}Y, ^{161}Tb, ^{131}I and ^{177}Lu. The source and target were defined as a voxels group corresponding to its range of Hounsfield's units (RHU) in Attenuation Map of MOBY. The source was uniformly distributed inside each organ. Simulations were performed with GATE version 8.1, which is based on Monte Carlo code Geant4 version 10.01 p02, radiation transport was performed with the compressed matrix navigation method, because it is the best way to perform the simulation with low computing resources. GATE generates the simulation results in an image file that contains the information of Deposited Energy in each voxel (detector) inside the region of interest and unused values in the remain voxels of the phantom, all detectors had to be segmented using a mask developed in ImageJ to calculate the deposited energy in the region of interest (ROI).

2.3. Dosimetry

The absorbed dose in a source-target organ depends on the amount of cumulated activity ($\tilde{A}_h$) and S-value, as described in MIRD scheme, where the absorbed dose is defined as:

$$D = \tilde{A}_h . S(r_k \leftarrow r_h) \tag{1}$$

In general, $S(r_k \leftarrow r_h)$ is the absorbed energy per mass unit in the target organ r_k by the decay of the radionuclide present in the source organ r_h, but in this work source region is the target region. The S values calculations can be done by the following equation:

$$S_{(t\leftarrow s)} = 1.6x10^{10}\frac{\sum particle \sum_i (E_{dep})_i n_i}{m_t} \tag{2}$$

Where E_{dep} is the value in MeV of the energy deposited obtained by the Monte Carlo simulation, n_i is the number of particles per decay and m_t is the mass of the target organ(Kolbert et al., 2003).

The organ S-values were compared model to model, to get the *Percentage Change* (PC) between them for all three voxel models, where PC was calculated as follow,

$$PC = \left|\frac{(V_f - V_i)}{V_i}\right| * 100 \tag{3}$$

where V_f and V_i are final and initial values respectively, for changes male to female (m → f), V_f is for female and V_i is for male, and so on for male to MOBY (m → M) and female to MOBY (f → M).

The PC between absorbed doses were also analyzed to determine the importance of performing dosimetric calculations with the appropriate geometry for each gender, where initial radioactivity equal to 1Bq was used to obtain the cumulated activity.

2.4. Computing resources

Calculations were performed using a Intel Xeon 4-core, RAM 16 GB; archiving system 2 TB and the image segmentation and post processing with Inter i7 Quad core @2.6 GHz, RAM 16 GB, archiving system 2 TB and a video card Radeon Graphics.

3. Results

3.1. Organ masses

The average weight of the heart, spleen, kidneys and liver was found, their average values are shown in Table 1. A major difference between two models was found in kidneys and liver, a lighter difference in the spleen and similar dimensions in heart.

The MOBY's parameter file allows changes to be made to any “vol-organ parameter” or “whole body parameter”. The “vol-heart”, “vol-

Table 1
Comparison of organ weight in mice from females and males groups.

Females	Heart	Spleen	Kidneys	Liver
Average [g]:	0.2370 ± 0.0290	0.2049 ± 0.04877	0.2704 ± 0.02538	2.4551 ± 0.3175
Males	**Heart**	**Spleen**	**Kidneys**	**Liver**
Average: [g]	0.2372 ± 0.2030	0.1791 ± 0.01794	0.4040 ± 0.0563	3.112 ± 0.2849

Fig. 1. Simulations results showing hits in the region of interest.

spleen", "vol-kidney" and "vol-liver" parameters were modified and kept the rest of the organs without changes.

3.2. Simulation

During the simulation, GATE converts the HU values to the Geant4 material compositions to calculate the deposited energy within the voxels that share the same material composition and have an attached voxel detector, that resulting deposited energy is a consequence of the hits of the particles that released their energy in those voxels, as shown in Fig. 1, then it is necessary to perform a segmentation of voxels with a HU range defined for tissue of interest.

The output is an Image file that had to be post processed in order to separate the information of the region of interest, a mask with the same dimensions of the region of interest was implemented for each organ using ImageJ, then S values for each organ was obtained.

3.3. S values

S values for ten radionuclides were obtained for each organ for all three models, those values are shown in Table 2.

According to Table 2, for each radionuclide the effect on the S value of the organ mass is noticeable, the magnitude of this effect depends on the organ.

3.4. Dosimetry

As well as the S values, the absorbed dose was obtained and presented in Table 3. The PC in absorbed dose (***D***) values were not as in the S values, because ***D*** also depends on half-life of radionuclides.

In order to verify the effect of the scaling of the organs in the phantoms on the absorbed dose a comparison between the three models was made, there was noticed that the organs with a major mass difference such as the kidneys and the liver present a major dispersion in the PC.

4. Discussion

The S values are necessary to obtain the internal absorbed dose according to eq. (1), so other works have reported S values for different radionuclides and sizes of mouse phantoms(Bitar et al., 2007a, 2007b; Kostou et al., 2016; Taschereau and Chatziioannou, 2007)(Xie and Zaidi, 2013), in order to assess the potential of new radiopharmaceuticals. Nevertheless, to perform a more accurate dosimetry it

Table 2
S values for different radionuclides for three mouse models.

Organ	Model	S values $\left(\frac{Gy}{Bq \cdot s}\right)$									
		^{67}Ga	^{68}Ga	^{18}F	^{131}I	^{99m}Tc	^{90}Y	^{223}Ra	^{166}Ho	^{177}Lu	^{161}Tb
Kidneys	Male	1.06E-06	3.41E-12	6.29E-11	3.48E-11	3.42E-11	1.49E-10	1.59E-10	3.01E-11	5.35E-11	6.16E-11
	Female	2.19E-06	3.65E-12	1.65E-10	5.87E-11	6.94E-11	3.84E-10	2.34E-10	2.12E-11	2.89E-11	3.39E-11
	MOBY	2.75E-06	4.08E-12	1.77E-10	5.93E-11	7.19E-11	4.05E-10	2.66E-10	1.84E-11	1.55E-11	3.28E-11
Spleen	Male	1.85E-09	3.88E-14	1.81E-10	1.88E-10	8.18E-11	4.03E-10	3.90E-10	8.93E-11	1.39E-10	1.65E-10
	Female	1.69E-09	4.05E-14	1.75E-10	1.54E-10	7.94E-11	3.96E-10	3.92E-10	8.96E-11	1.45E-10	1.66E-10
	MOBY	1.54E-09	4.01E-14	1.78E-10	1.60E-10	8.03E-11	3.98E-10	3.93E-10	8.95E-11	1.44E-10	1.69E-10
Liver	Male	2.62E-10	3.20E-11	1.42E-11	6.54E-13	6.40E-14	4.06E-11	3.66E-11	7.49E-12	3.45E-13	2.17E-11
	Female	3.20E-10	3.63E-11	1.62E-11	7.49E-13	7.56E-14	4.66E-11	2.94E-11	6.34E-12	2.33E-13	2.04E-11
	MOBY	2.94E-10	3.59E-11	1.58E-11	7.52E-13	7.61E-14	4.75E-11	2.89E-11	6.26E-12	1.97E-13	1.96E-11
Heart	Male	1.55E-09	1.33E-10	7.75E-11	8.74E-11	9.85E-11	1.96E-10	1.66E-10	3.65E-11	7.88E-11	6.65E-11
	Female	1.55E-09	1.32E-10	7.73E-11	8.72E-11	9.78E-11	1.98E-10	1.67E-10	3.67E-11	7.85E-11	6.60E-11
	MOBY	1.48E-09	1.31E-10	7.72E-11	8.69E-11	7.65E-11	2.04E-10	1.64E-10	3.69E-11	7.84E-11	6.61E-11

Table 3
Absorbed dose calculated for the three mouse models using different radionuclides.

Organ	Model	Absorbed dose (Gy)									
		^{67}Ga	^{68}Ga	^{18}F	^{131}I	^{99m}Tc	^{90}Y	^{223}Ra	^{166}Ho	^{177}Lu	^{161}Tb
Kidneys	Male	4.28E-01	2.00E-08	5.98E-07	8.70E-05	1.07E-06	4.96E-05	5.66E-04	4.19E-06	1.11E-04	1.32E-04
	Female	8.85E-01	2.14E-08	1.57E-06	1.47E-04	2.16E-06	1.28E-04	8.33E-04	2.95E-06	5.98E-05	7.28E-05
	MOBY	1.11E-01	2.39E-08	1.68E-06	1.48E-04	2.24E-06	1.35E-04	9.47E-04	2.56E-06	3.21E-05	7.04E-05
Spleen	Male	7.48E-04	2.27E-10	1.72E-06	4.70E-04	2.55E-06	1.34E-04	1.39E-03	1.24E-05	2.88E-04	3.54E-04
	Female	6.83E-04	2.37E-10	1.66E-06	3.85E-04	2.47E-06	1.32E-04	1.40E-03	1.25E-05	3.00E-04	3.56E-04
	MOBY	6.22E-04	2.35E-10	1.69E-06	4.00E-04	2.50E-06	1.33E-04	1.40E-03	1.25E-05	2.98E-04	3.63E-04
Liver	Male	1.06E-04	1.88E-07	1.35E-07	1.63E-06	1.99E-09	1.35E-05	1.30E-04	1.04E-06	7.14E-07	4.66E-05
	Female	1.29E-04	2.13E-07	1.54E-07	1.87E-06	2.36E-09	1.55E-05	1.05E-04	8.83E-07	4.82E-07	4.38E-05
	MOBY	1.19E-04	2.10E-07	1.50E-07	1.88E-06	2.37E-09	1.58E-05	1.03E-04	8.72E-07	4.08E-07	4.21E-05
Heart	Male	6.26E-04	7.80E-07	7.36E-07	2.18E-04	3.07E-06	6.53E-05	5.91E-04	5.09E-06	1.63E-04	1.43E-04
	Female	6.26E-04	7.74E-07	7.35E-07	2.18E-04	3.05E-06	6.59E-05	5.95E-04	5.11E-06	1.62E-04	1.42E-04
	MOBY	5.98E-04	7.68E-07	7.34E-07	2.17E-04	2.38E-06	6.79E-05	5.84E-04	5.14E-06	1.62E-04	1.42E-04

is necessary to use real masses and volumes of organs because the variation of S value is dependent of organ mass. In the previously reported data, organ weights were obtained by resizing the entire phantom(Keenan et al., 2010; Xie and Zaidi, 2013), but these are not corresponding to the real masses of CD-1 mice obtained in this work. The mass difference between 35 g MOBY model and our female mouse phantom (34.4 g) was 30, 23, 37 and 22.5% for heart, spleen, kidneys and liver respectively, even when both models have almost the same weight.

The validation of our GATE/GEANT4 code domain was performed by running a simulation with a 30 g whole body mouse model (MOBY) and comparing the results with the S values reported by (Keenan et al., 2010; Kostou et al., 2016) for fluorine-18 because this radionuclide is defined as standard in the GATE libraries, the self-absorbed S values results seem to be in good agreement with differences varying between 3 and 7%.

The self-absorbed S values for heart, spleen, kidneys and liver in the female-(34.4 g), male-(40 g) and MOBY(35 g) phantom models present changes among them due to the volume variations described above. These changes are more noticeable in the kidneys and liver (Table 2). For (m → f) comparison, the S values for the liver have Percentage Changes up to 32.4% for ^{177}Lu, considering the ten radionuclides an average *Percentage Change* (PC) of 17.05 ± 6.9 was obtained. In kidneys a PC up to 162.32% for ^{18}F and 157.71% for ^{90}Y was found, even when they are radionuclides for diagnosis and treatment respectively. In this case an average PC of 77.29 ± 53.16 was obtained.

Regarding the changes between MOBY standard phantom with female and male models, it was observed that MOBY and the female model have similar volumes and masses organ and whole body, therefore calculating changes female to MOBY (f → M) the percentage changes are smaller than changes male to MOBY (m → M). In accordance with eq. (1), the dosimetric percentage changes remain as those of the S values.

It is worth mentioning that the biggest difference between the female and male models predominates, this indicates that in the internal dosimetry the use of a customized geometry is relevant for each gender and a standard model is not a good choice because there can be errors greater than 100% when performing dosimetry.

5. Conclusions

The size organ differences between male and female phantoms can not be obtained only by rescaling the whole MOBY phantom, it is necessary to rescale organ by organ, keeping the full phantom size fixed. The effect on the dosimetry of the organ size within a voxel phantom was investigated, using three models representing mass differences of the organs between females and males CD-1 mice and the standard MOBY model (35 g). The geometry impact on the self-absorbed S value can produce errors greater than 100% in the dosimetric calculations, this indicates that in the internal dosimetry the use of a customized geometry is relevant for each gender and a standard model is not a good choice.

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